Receptors for gammaglobulin in the central and peripheral nervous system

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A heterogeneous group of receptors binding the Fc region of immunoglobulin (Ig), Fc receptors provide important links between the cellular and the humoral branches of the immune system. The members of this receptor group, specific for essentially all the Ig isotypes, are expressed on a variety of cells and mediate multiple important functions.

Receptors for IgG (FcγR), a subgroup within the larger group of Fc receptors, belong to the Ig supergene family. The receptors have repeating extracellular domains, a membrane spanning portion and a cytoplasmic tail and the genes encoding the receptors have been assigned to chromosome 1.

When FcγR interact with the ligand, causing crosslinking of the receptors, a variety of biological responses are triggered. These include phagocytosis, antibody-dependent cellular cytotoxicity (ADCC), release of cytotoxic and inflammatory mediators, enhanced antigen presentation, immune regulation and transfer of IgG. For immune regulation, it has been shown that the FcγR can interfere with maturation of T and B lymphocytes as well as antibody production in an isotypic specific way.

Three major classes of leucocyte FcγR are currently recognised on the basis of ligand affinity, reactivity with monoclonal antibodies (mAbs) and cloning of complementary DNA (cDNA). FcγRI (CD64) are 70 kDa molecules expressed on monocytes and macrophages with high affinity for IgG and can be induced on neutrophils by interferon-γ (IFN-γ). FcγRII (CD32) have a molecular weight of 40 kDa and are encoded by three genes. FcγRIIB are expressed on lymphocytes, FcγRIIA and FcγRIIC are expressed on neutrophils, while monocytes and macrophages express all three variations. FcγRIII (CD16), of molecular weight between 45–80 kDa, have two distinct forms. FcγRIIB found on neutrophils are anchored to the membrane by glycosyl-phosphatidyl inositol whereas FcγRIIA expressed on natural killer (NK) cells and macrophages are transmembrane proteins. Both FcγRII and FcγRIII have low affinity for IgG. Current information indicates that the three classes of FcγR do not perform discrete tasks. Rather, their functions seem dictated by the cell type on which they are displayed.

FcγR are also present on non-lymphoid cells in different organs, for example on trophoblasts and endothelial cells in human placenta and on keratinocytes in human skin. In this review we report the presence and possible functions of FcγR in the human nervous system.

**FcγR in the central nervous system**

FcγR have been demonstrated on cells in the choroid plexus, arachnoid granulations, leptomeninges, perivascular macrophages, microglia and on endothelial cells. FcγR have also been found on microglia in culture. The receptors were demonstrated by haemadsorption of IgG-coated indicator cells, by binding of soluble immune complexes of horseradish peroxidase (HRP) anti-HRP and serologically using mAbs. Microglia and perivascular macrophages were stained by mAbs to FcγRI, FcγRII and FcγRIII, whereas endothelial cells were stained by anti-FcγRIII mAbs only. Oligodendrocytes, astrocytes and neurons do not express FcγR. Recently, FcγRIII mRNA was demonstrated in microglia using in situ hybridisation. The same radiolabelled cDNA probe for FcγRIII hybridised with a 1.4 kb RNA band in Northern blots prepared from total RNA from brain, indicating that the receptors are produced in the CNS.

**FcγR in the peripheral nervous system**

FcγR have also been demonstrated on Schwann cells, perineurial cells, endothelial cells and on scattered endoneurial macrophages. The receptors were found on the surface membrane, inner membrane (axolemma) and on vesicles within the cytoplasm of Schwann cells by electron microscopy. Schwann cells in culture apparently lose their FcγR expression. Whether this is due to dedifferentiation of the cells or to loss of Schwann cell—axon interaction is not known. FcγR have been recognised in fetal nerves at approximately 10 weeks of gestation showing that the receptors are an innate component of the PNS. Mabs against FcγRI, FcγRII and FcγRIII stained scattered endoneurial macrophages, whereas only mAbs against low affinity FcγR stained Schwann cells, perineurial cells and endothelial cells. A radiolabelled cDNA probe for FcγRIII hybridised with a 1.4 kb RNA band in Northern blots prepared from total RNA from peripheral nerve. The steady state level of the 1.4 kb FcγRIII mRNA was found to be developmentally regulated by densitometry. In situ hybridisation experiments have demonstrated increased numbers of endoneurial FcγRII mRNA positive macrophages in Wallerian degeneration, and in experimental allergic neuritis (EAN).

**Functions of FcγR in the nervous system**

To date little is known about the functions of FcγR in the CNS and PNS. The FcγR in the...
choroidal plexus and arachnoid granulations may be involved in the transcellular transport of IgG from blood to cerebrospinal fluid (CSF) and from CSF to blood, the same mechanism proposed for FcyR in the placenta transferring IgG from mother to fetus.2

FcyR on microglia mediate phagocytosis of IgG-coated particles, ADCC and oxidative burst.3 Crosslinking of microglial FcyR may also induce production of inflammatory mediators such as interleukin-1, interleukin-6 and tumour necrosis factor. Recently, it has been shown that FcyR expression is highly upregulated on perivascular macrophages and microglia within active multiple sclerosis (MS) lesions compared with FcyR expression on cells in the parenchyma outside the demyelinating lesions.3 FcyR therefore probably play an important role in myelin breakdown in MS. IFN-γ greatly enhances microglia FcyR mediated responses.7 This is of particular interest since MS patients treated with IFN-γ experience exacerbation.15 FcyR may also contribute to immune-mediated phagocytosis by leptomeningeal cells which have the potential to become phagocytic during pathological conditions.16

Immune-mediated phagocytosis and antigen presentation may also take place in the PNS,17,18 via FcyR on Schwann cells and on endoneurial macrophages. Increased number of macrophages participating in phagocytosis are found in Wallerian degeneration19 and in EAN.14 Whether crosslinking of FcyR on cells in the PNS also mediates release of various cytokines, as well as lymphosol enzymes, remains to be determined.

FcyR on cells in the CNS and PNS may furthermore enhance infection of opsonised agents, such as HIV in microglia20 and M. leprae in Schwann cells.20 In addition, FcyR on endothelial cells may be involved in binding immune complexes and induce vasculitis.

Binding of IgG to FcyR induces production of soluble FcyR (sFcyR) in vitro.21 This may explain sFcyR intercellularly in MS lesions. sFcyR may neutralise possible hazardous autoantibodies by preventing membrane-binding or by blocking the CIq site which again would limit complement activation. Since sFcyR block in vitro IgG production,20 it is possible that soluble receptors also reduce the production of autoantibodies in the nervous system.

Conclusions

FcyR are present on various cells in the CNS and PNS. The different biological functions of these receptors may be relevant in the pathogenesis of immunemediated diseases of the nervous system. Therapeutic trials with intravenous IgG have shown clinical improvement in patients with neurological diseases such as Guillain-Barré syndrome and chronic inflammatory demyelinating polynuropathy.24 Recently, it has been shown that infusions of Fcy fragments are beneficial in immune thrombocytopenic purpura,25 indicating that ligand binding to FcyR may induce immuno-suppressive effects. This could occur systemically and locally in the nervous system through a damaged blood-brain or blood-nerve barrier. Binding of IgG Fc fragments to FcyR in the CNS and PNS could: 1) block the various effects that are mediated by crosslinked FcyR such as phagocytosis, enhanced antigen presentation, ADCC and release of cytokotic and inflammatory mediators; and 2) release sFcyR that may neutralise autoantibodies or immune complexes and downregulate a local Ig production.


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